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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/117,218	01/11/1999	SUSANNE M. BROWN	117-261	3436

7590 01/16/2004

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 01/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM

Office Action Summary	Application No.	Applicant(s)	
	09/117,218	BROWN ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33 and 37-40* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33 and 37-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/15/03 has been entered.

Amended claims 33 and 37-40 are pending in the present application, and they are examined on the merits herein.

Information Disclosure statement

The Information Disclosure Statement and one reference submitted to the Office on June 2/2003 are not present in the application. Applicants are requested to send copies of the aforementioned IDS and the reference.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 33 and 37-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Martuza et al. (U.S. Patent No. 6,139,834 with the effective filing date of June 23, 1994; Cited previously) in view of Brown et al. (WO 92/13943 with a publication date of August 20, 1992; PTO-1449, IDS). **This is a modified rejection.**

The claims are drawn to a method of treating a non-neuronal cancer in a mammal, said method comprises the step of injecting a mammal intratumorally with an effective amount of a mutant herpes simplex virus HSV 1716, and wherein said mutant virus infects, replicates and lyses the non-neuronal tumor cells of said cancer in said mammal, and thereby treating the non-neuronal cancer.

Martuza et al. teach the use of a replication-competent viral vector, preferably a herpes simplex virus, suitable for use in humans, that is capable of killing human tumor cells *in vivo*, that exhibits hypersensitivity to anti-viral agents and an inability to revert to wild-type virus, and that is not neurovirulent at a dose required to kill tumor cells (see col. 3, lines 10-17; col. 4, lines 14-22). Martuza et al. also teach that viruses have been

tested in the prior art for their ability to treat various types of tumors in animals and humans via direct cell killing by the virus, called oncolysis, and that for use as antineoplastic agents these viruses have been genetically altered so that they are not capable of replication in non-dividing cells to avoid systemic infection (see col. 1, line 44 continues to line 5 of col. 2). **In a preferred embodiment**, Martuza et al. teach the delivery of a pharmaceutical composition comprising: (A) a herpes simplex virus vector that is altered in (i) the γ34.5 gene, and (ii) the ribonucleotide reductase gene; and (B) a pharmaceutically acceptable vehicle for said vector, such that said tumor cells are altered *in situ* by said vector, whereby said tumor cells are killed; the same method wherein said tumor cells are selected from the group consisting of melanoma cells, pancreatic cancer cells, prostate carcinoma cells, lymphoma cells, hepatoma cells and mesothelioma and epidermoid carcinoma cells (See the entire patent and particularly claims 1and 3). An exemplary mutant herpes simplex virus, G207, disclosed by Martuza et al. contains a 1-kB deletion in both copies of the γ34.5 gene within the BamH1 fragment of the long terminal repeat of the viral genome (See Figures 1, 2 and column 15, lines 36-45). The mutant herpes simplex virus can be derived from either HSV-1 or HSV-2 (column 4, lines 20-22; column 7, lines 6-22; column 8, lines 5-7). The mutant herpes simplex virus can be administered to human and non-human animals suffering from tumors and neoplasms by direct intraneoplastic inoculation (column 11, lines 45-57). Moreover, the disclosed method for killing tumors and neoplasms is not necessarily limited to malignant brain tumor, such as astrocytoma, glioblastoma and others (column 11, lines 45-55; column 3, lines 61-67).

Martuza et al. do not teach specifically a method of killing non-neuronal tumor cells in a mammal using the mutant herpes simplex virus strain 1716.

Brown et al. already disclose HSV-1 mutant 1716 and that strain 1716 contains a 759 bp deletion in each copy of the γ34.5 gene which is found within the BamH1 s fragment of the long repeat region of the viral genome (See page 4, lines 16-31 in Brown et al.). The deletion is associated with the non-neurovirulence (replication defect in the central nervous neuron environment) *in vivo* for strain 1716 comparing to the parental wild type strain, even though strain 1716 grows as efficiently as the wild type 17+ virus (example 4, pages 20-21). Furthermore, Brown et al. teach that strain 1716 has a vaccine potential because it is incapable of replicating in CNS neurons but is capable to elicit a good immunological and cell mediated response due to its ability to replicate in the peripheral tissue (page 3, lines 7-11).

Accordingly, it would have been obvious to one of ordinary skilled in the art at the time of invention was made to utilize the mutant herpes simplex virus strain 1716 taught by Brown et al. in the method disclosed by Martuza et al. to treat non-neuronal cancer in a mammal. This is because the mutant virus strain 1716 is capable of killing non-neuronal tumor cells via oncolysis since it still retains the ability to replicate in the peripheral tissues, yet it is non-neurovirulent, and safe as it is also taught to be used as an attenuated live vaccine by Brown et al. Additionally, the mutant virus strain 1716 is still sensitive to acyclovir and ganciclovir because it still retains the thymidine kinase gene.

One of ordinary skilled artisan would have been motivated to carry out the above modification for the advantages offered by the mutant virus strain 1716 as discussed immediately above.

One would also have a reasonable expectation of success to carry out the above modification in light of the teachings of Martuza et al. and Brown et al., coupled with a high level of skills of an ordinary skilled artisan at the effective filing date of the present application.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Responses to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on December 15, 2003 (pages 4-8) have been fully considered, but they are not found persuasive.

Applicants argue basically that although WO 92/13943 discloses the mutant HSV 1716 but it does not teach the mutant could be used in the treatment of non-neuronal cancers. Martuza discloses the use of a mutant HSV for the treatment of non-neuronal cells, however, the mutant is not only a different strain (strain F from strain 17 of HSV1716), but further is a different mutant (gamma34.5 and RR gene null mutant). Applicants further argue that there is no motivation for the skilled person to choose the very specific mutant HSV1716 to combine with the teaching of Martuza, given the

existence of many hundreds of thousands of HSV strains, and a number of HSV mutant strains, and that there is no reasonable expectation of success.

The examiner notes that this is a 103(a) rejection, and therefore a single reference is not required to teach every element of the claims. Martuza teaches clearly the use of a replication-competent viral vector, preferably a herpes simplex virus, suitable for use in humans, that is capable of killing human tumor cells *in vivo*, that exhibits hypersensitivity to anti-viral agents and an inability to revert to wild-type virus, and that is not neurovirulent at a dose required to kill tumor cells (see col. 3, lines 10-17; col. 4, lines 14-22). The gamma34.5 and RR gene null mutant herpes simplex virus is only **a preferred embodiment** of Martuza's teachings. One of ordinary skilled artisan would have been motivated to carry out the above modification because the mutant virus strain 1716 is capable of killing non-neuronal tumor cells via oncolysis since it still retains **the ability to replicate in the peripheral tissues**, yet it is **non-neurovirulent**, and **safe** as it is also taught to be used as an attenuated live vaccine by Brown et al. Additionally, the mutant virus strain 1716 **is still sensitive** to acyclovir and ganciclovir because it still retains the thymidine kinase gene. Examiner further notes that the replication defect of the mutant HSV 1716 only manifests in the central nervous system neuronal environment, and therefore allowing the mutant HSV 1716's ability to kill non-neuronal tumor cells via oncolysis and its neuronal avirulent property (all of which are desirable properties of a mutant HSV for treating a non-neuronal cancer in a mammal). Furthermore, in light of the teachings of Martuza et al. and Brown et al., coupled with a high level of skills of an ordinary skilled artisan at the effective filing date of the present

application, it is unclear why one would not have a reasonable expectation of success for using the mutant HSV 1716 in killing non-neuronal cancer cells, particularly strain 1716 grows (or replicates) as efficiently as the wild type 17+ virus (see Brown et al., example 4, pages 20-21).

Accordingly, amended claims 33 and 37-40 are rejected under 35 U.S.C. 103(a) for the reasons set forth above.

Amended claims 33 and 37-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roizman et al. (U.S. Patent No. 6,340,673; Cited previously) in view of Brown et al. (WO 92/13943 with a publication date of August 20, 1992; PTO-1449, IDS) and Martuza et al. (U.S. Patent No. 6,139,834 with the effective filing date of June 23, 1994; Cited previously). **This is a modified rejection.**

Roizman et al. teach using an HSV-1 virus with a specific mutation in the gamma 35.4 gene to treat cancer and tumorogenic diseases both in the CNS and in all other parts of the body in a mammal including human, not necessarily limited to tumors of the CNS (see col. 5, lines 63-66; col. 9, lines 50-61; and the claims). Roizman et al. further teach direct injection of the virus into the tumor or intratumorally, and that **an exemplified HSV-1 virus** with a specific mutation in the gamma 35.4 gene is the recombinant virus R3617 or R3616 lacking 1kb of DNA in each copy of the gamma 34.5 gene (see Table 1 of col. 17; Fig. 2). Roizman et al. also teach that infection of cells of neuronal origin with mutants incapable of expressing the gamma 34.5 gene resulted in shutoff of cellular protein synthesis, whereas infection of cells of non-neuronal origin

with wild type or mutant viruses resulted in sustained protein synthesis and production of infectious progeny (col. 18, lines 10-15).

Roizman et al. do not specifically teach a method for treating a non-neuronal cancer in a mammal using the mutant herpses simplex virus strain 1716 or wherein the cancer is a mesothelioma, ovarian carcinoma, bladder cancer or melanoma.

However, at the effective filing date of the present application, Brown et al. already disclose HSV-1 mutant 1716 and that strain 1716 contains a 759 bp deletion in each copy of the γ34.5 gene which is found within the BamH1 s fragment of the long repeat region of the viral genome (See page 4, lines 16-31 in Brown et al.). The deletion is associated with the non-neurovirulence (replication defect in the central nervous neuron environment) *in vivo* for strain 1716 comparing to the parental wild type strain, even though strain 1716 grows as efficiently as the wild type 17+ virus (example 4, pages 20-21). Furthermore, Brown et al. teach that strain 1716 has a vaccine potential because it is incapable of replicating in CNS neurons but is capable to elicit a good immunological and cell mediated response due to its ability to replicate in the peripheral tissue (page 3, lines 7-11). Moreover, Martuza et al. already teach the use of a replication-competent viral vector, preferably a herpes simplex virus, suitable for use in humans, that is capable of killing human tumor cells *in vivo*, including mesothelioma, melanoma and others, that exhibits hypersensitivity to anti-viral agents and an inability to revert to wild-type virus, and that is not neurovirulent at a dose required to kill tumor cells (see col. 3, lines 10-17; col. 4, lines 14-22).

Accordingly, it would have been obvious to one of ordinary skilled in the art at the time of invention was made to utilize the mutant herpes simplex virus strain 1716 taught by Brown et al. to treat a non-neuronal cancer, including mesothelioma or melanoma, in a mammal in light of the teachings of Roizman et al. and Martuza et al. This is because the mutant virus strain 1716 is capable of killing non-neuronal tumor cells via oncolysis since it still retains the ability to replicate in the peripheral tissues, yet it is non-neurovirulent, and safe as it is also taught to be used as an attenuated live vaccine by Brown et al. Additionally, the mutant virus strain 1716 is still sensitive to acyclovir and ganciclovir because it still retains the thymidine kinase gene.

One of ordinary skilled artisan would have been motivated to carry out the above modification for the advantages offered by the mutant virus strain 1716 as discussed immediately above.

One would also have a reasonable expectation of success to carry out the above modification in light of the teachings of Roizman et al., Martuza et al. and Brown et al., coupled with a high level of skills of an ordinary skilled artisan at the effective filing date of the present application.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Responses to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on December 15, 2003 (pages 4-8) have been fully considered, but they are not found persuasive.

Applicants argue basically that Roizman teaches the use of a different mutated strain (strain F instead of strain 17 of HSV 1716), along with various arguments (e.g., lack of motivation, and reasonable expectation of success) already set forth above.

Once again, the examiner notes that this is a 103(a) rejection, and therefore a single reference is not required to teach every element of the claims. Roizman teaches clearly the use of an HSV-1 virus with a specific mutation in the gamma 35.4 gene to treat cancer and tumorogenic diseases both in the CNS and in all other parts of the body in a mammal including human, not necessarily limited to tumors of the CNS (see col. 5, lines 63-66; col. 9, lines 50-61; and the claims). Roizman et al. further teach direct injection of the virus into the tumor or intratumorally, and that **an exemplified HSV-1 virus** with a specific mutation in the gamma 35.4 gene is the recombinant virus R3617 or R3616 lacking 1kb of DNA in each copy of the gamma 34.5 gene (see Table 1 of col. 17; Fig. 2). One of ordinary skilled artisan would have been motivated to carry out the above modification because the mutant virus strain 1716 is capable of killing non-neuronal tumor cells via oncolysis since it still retains **the ability to replicate in the peripheral tissues**, yet it is **non-neurovirulent**, and **safe** as it is also taught to be used as an attenuated live vaccine by Brown et al. Additionally, the mutant virus strain 1716 **is still sensitive** to acyclovir and ganciclovir because it still retains the thymidine kinase

gene. Examiner further notes that the replication defect of the mutant HSV 1716 only manifests in the central nervous system neuronal environment, and therefore allowing the mutant HSV 1716's ability to kill non-neuronal tumor cells via oncolysis and its neuronal avirulent property (all of which are desirable properties of a mutant HSV for treating a non-neuronal cancer in a mammal). In light of the teachings of Roizman et al., Martuza et al. and Brown et al., coupled with a high level of skills of an ordinary skilled artisan at the effective filing date of the present application, it is unclear why one would not have a reasonable expectation of success for using the mutant HSV 1716 in killing non-neuronal cancer cells, particularly strain 1716 grows (or replicates) as efficiently as the wild type 17+ virus (see Brown et al., example 4, pages 20-21).

Accordingly, amended claims 33 and 37-40 are rejected under 35 U.S.C. 103(a) for the reasons set forth above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Amended claims 33 and 37-40 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 51 of the copending Application No. 08/776350. Although the conflicting claims are not identical, they are not patentably distinct from each other because a method of treating a non-neuronal cancer in a mammal comprising the step of injecting a mammal intratumorally with an effective amount of a mutant herpes simplex virus HSV 1716 of the instant application **reads on** a method of treating a metastatic tumor which occurs in but does not originate from the central nervous system of a human comprising intratumoral or intracranial injection of a HSV-1, wherein said HSV-1 is the mutant virus strain 1716 and wherein said HSV-1 infects and replicates within the tumor cells of the tumor. This is because the species or sub-genus (intratumoral or intracranial injection of HSV 1716 in a human to treat a metastatic tumor occurring in but does not originate from the central nervous system of a human) claimed in the conflicting application anticipates the claimed genus in the application being examined and, therefore a patent to the genus (intratumoral injection of HSV 1716 in a mammal to treat a non-neuronal cancer) would, necessarily, extend the rights of the species or sub-genus should the genus issue as a patent after the species or sub-genus.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339 or (571) 272-0776 after January 13, 2004.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (703) 308-1906, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

Quang Nguyen, Ph.D.

JAMES KETTER
PRIMARY EXAMINER